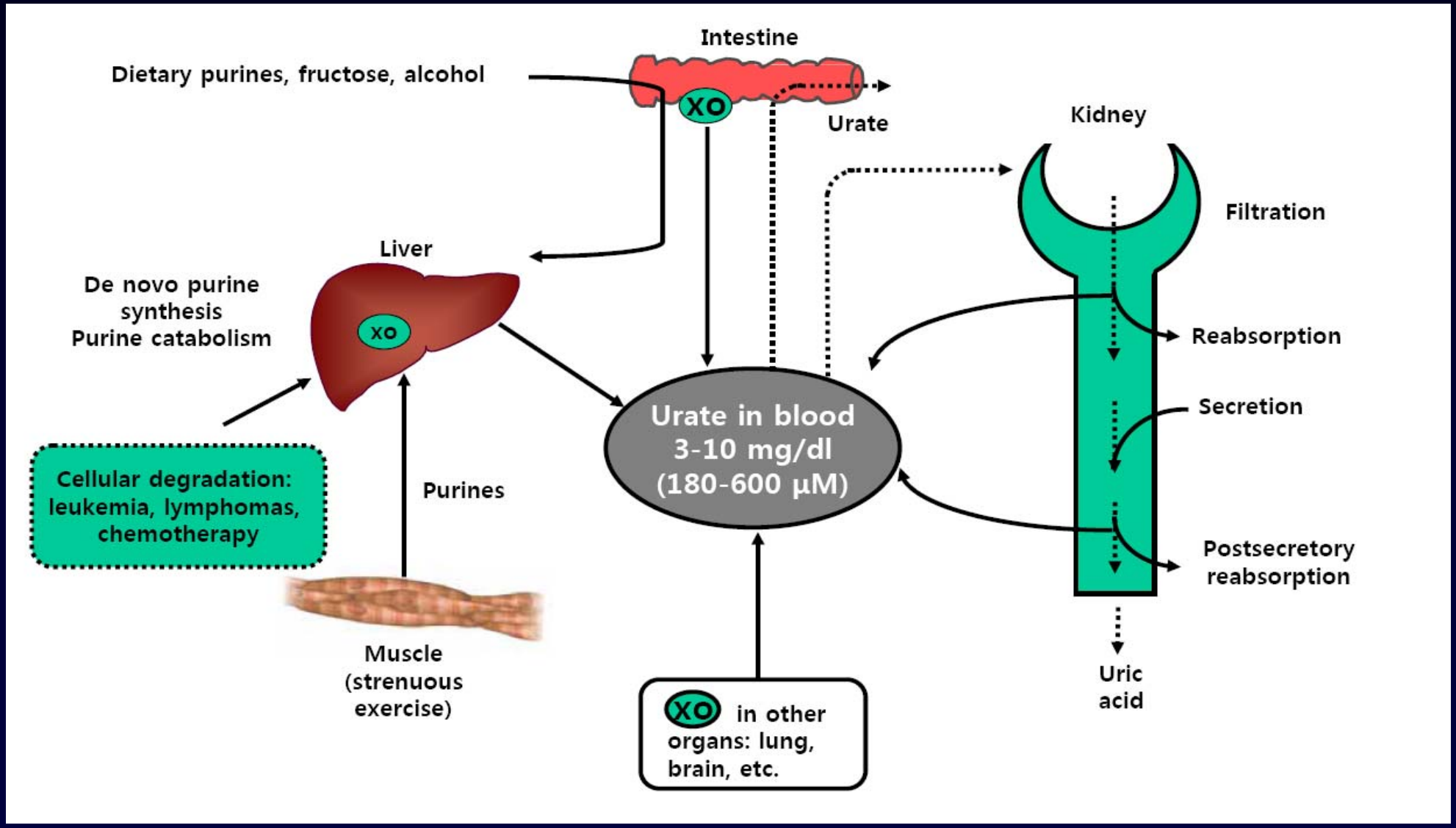
The significance of uric acid in hypertensive treatment

Seok-Min Kang, MD, Ph D.

Division of Cardiology,
Severance Cardiovascular hospital,
Yonsei University College of Medicine,
Seoul, Korea

Uric Acid


Intestine
Dietary purines, fructose, alcohol
XO
Urate
Kidney
Filtration
Liver
De novo purine synthesis
Purine catabolism
XO
Reabsorption
Secretion
Urate in blood
3-10 mg/dl
(180-600 μM)
Cellular degradation:
leukemia, lymphomas,
chemotherapy
Purines
Postsecretory reabsorption
Muscle
(strenuous exercise)
Uric acid
XO in other organs: lung, brain, etc.

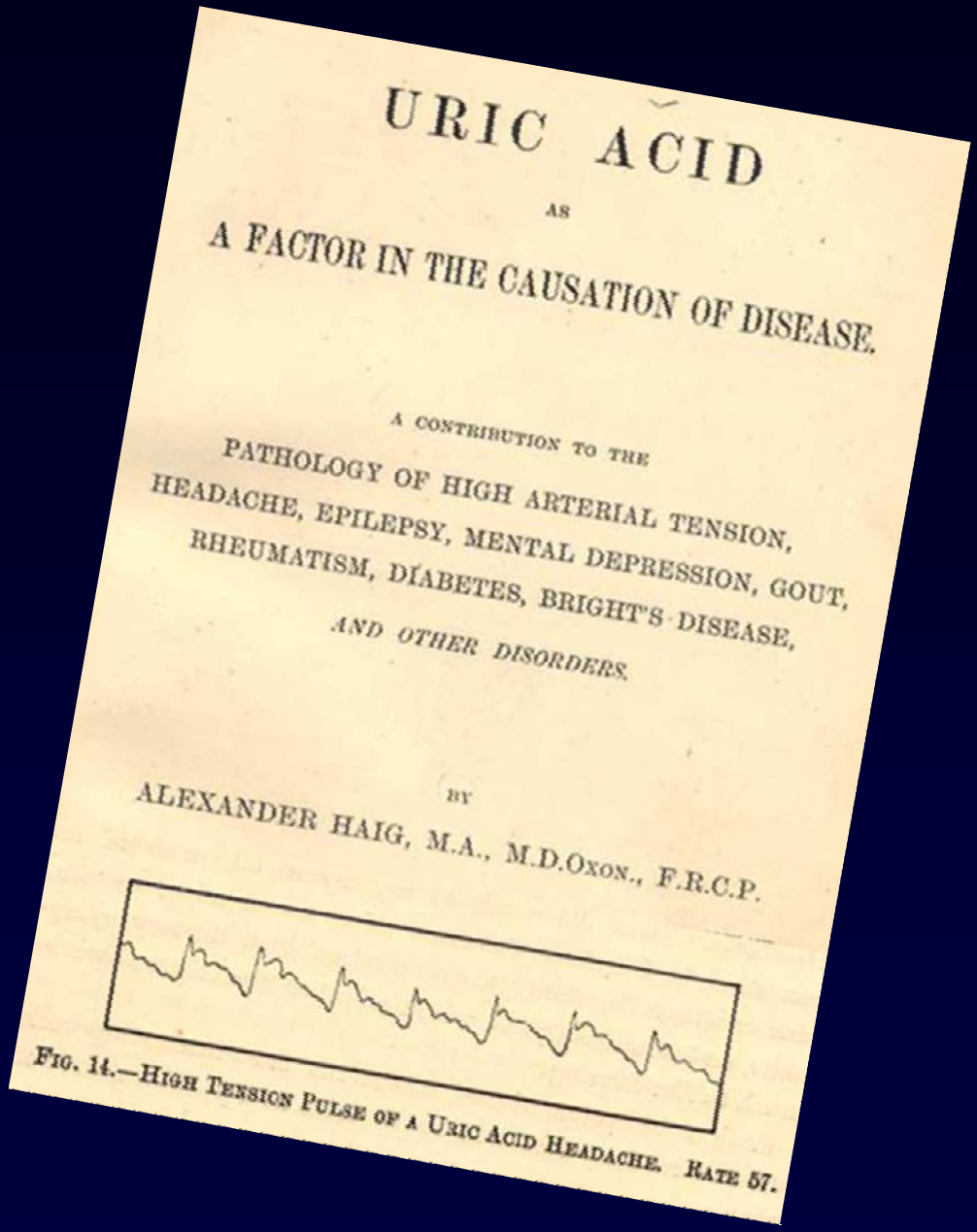
History

Mahomed FA

Prealbuminuric chronic Bright's disease

" *Uric acid* was first associated with primary hypertension "

Mahomed FA. Med Chir Trans, 1874
Mahomed FA. Lancet, 1879



URIC ACID

AS

A FACTOR IN THE CAUSATION OF DISEASE.

A CONTRIBUTION TO THE

PATHOLOGY OF HIGH ARTERIAL TENSION,
HEADACHE, EPILEPSY, MENTAL DEPRESSION, GOUT,
RHEUMATISM, DIABETES, BRIGHT'S DISEASE,

AND OTHER DISORDERS.

BY

ALEXANDER HAIG, M.A., M.D.OXON., F.R.C.P.

FIG. 14.—HIGH TENSION PULSE OF A URIC ACID HEADACHE. RATE 57.

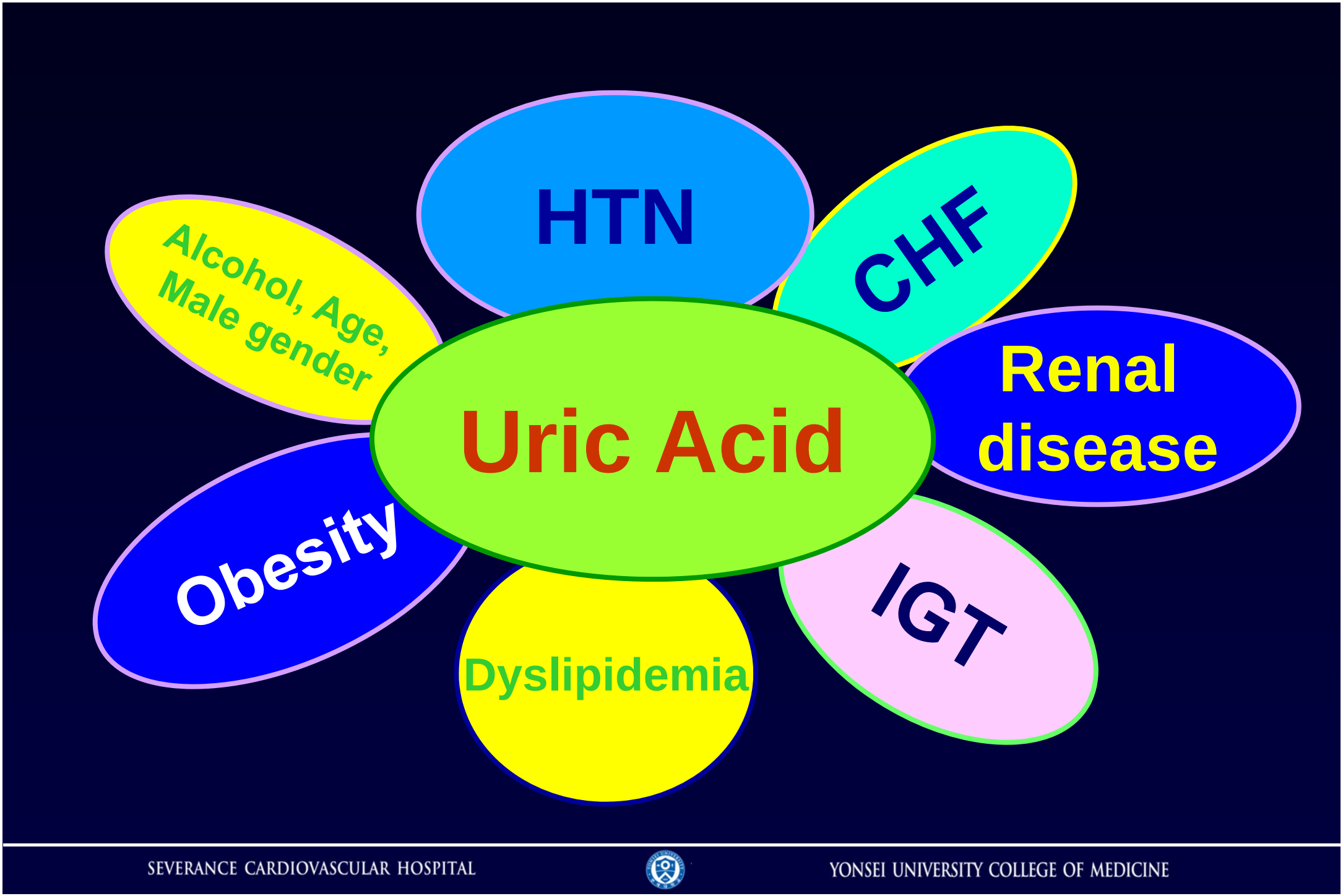
High-tension pulse of a uric acid headache

Haig A ,1892

Urodonal

:A treatment for lowering serum UA, treatment for arteriosclerosis and obesity

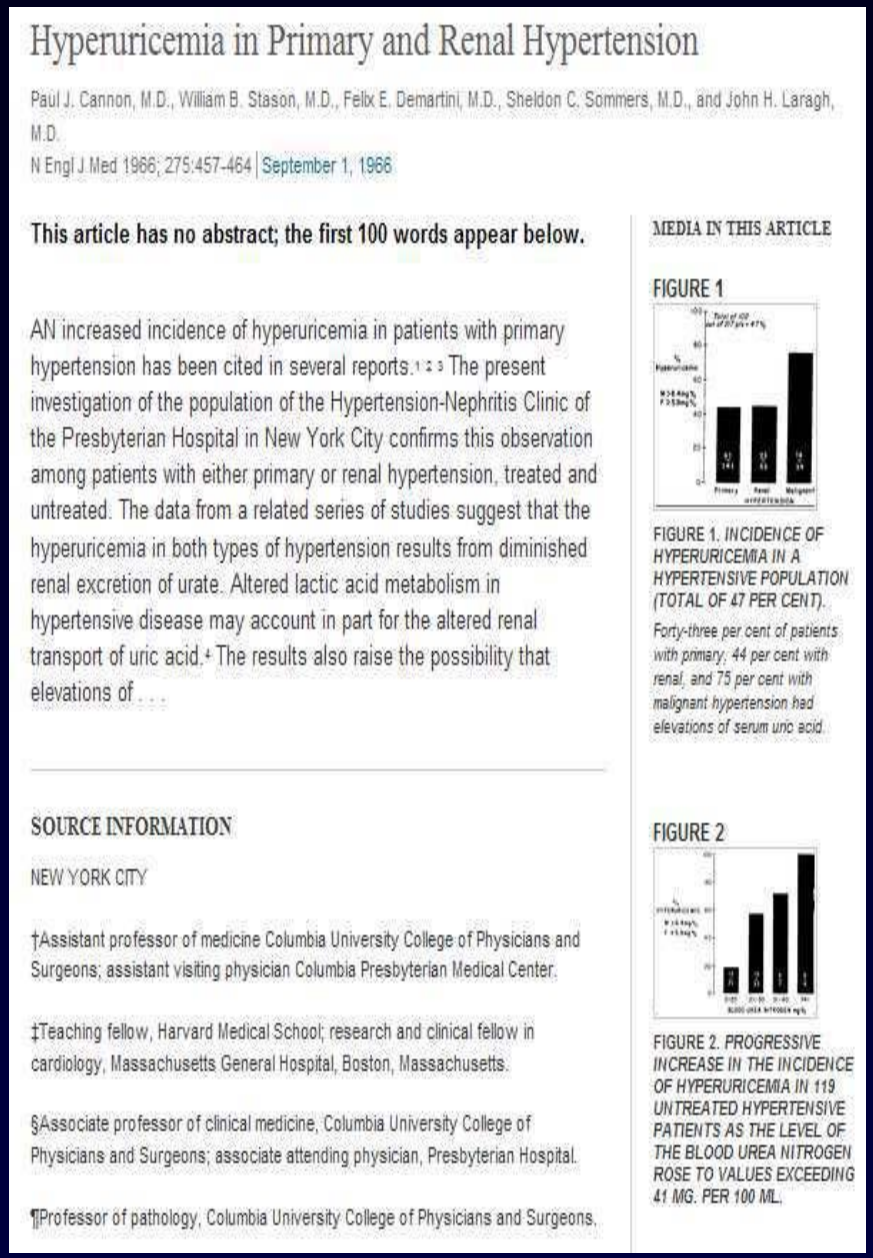
From French newspaper advertisement, Dec. 20th, 1919


HTN
CHF
Alcohol, Age, Male gender
Uric Acid
Renal disease
Obesity
Dyslipidemia
IGT

The Role of Uric Acid in HTN : Chicken or Egg ?

Uric acid is commonly elevated in patients with hypertension

Strong relationship between UA and HTN



Hyperuricemia in Primary and Renal Hypertension

Paul J. Cannon, M.D., William B. Stason, M.D., Felix E. Demartini, M.D., Sheldon C. Sommers, M.D., and John H. Laragh, M.D.

N Engl J Med 1966; 275:457-464 | September 1, 1966

This article has no abstract; the first 100 words appear below.

AN increased incidence of hyperuricemia in patients with primary hypertension has been cited in several reports.[1,2,3] The present investigation of the population of the Hypertension-Nephritis Clinic of the Presbyterian Hospital in New York City confirms this observation among patients with either primary or renal hypertension, treated and untreated. The data from a related series of studies suggest that the hyperuricemia in both types of hypertension results from diminished renal excretion of urate. Altered lactic acid metabolism in hypertensive disease may account in part for the altered renal transport of uric acid.[4] The results also raise the possibility that elevations of . . .

SOURCE INFORMATION

NEW YORK CITY

†Assistant professor of medicine Columbia University College of Physicians and Surgeons; assistant visiting physician Columbia Presbyterian Medical Center.

‡Teaching fellow, Harvard Medical School; research and clinical fellow in cardiology, Massachusetts General Hospital, Boston, Massachusetts.

§Associate professor of clinical medicine, Columbia University College of Physicians and Surgeons; associate attending physician, Presbyterian Hospital.

¶Professor of pathology, Columbia University College of Physicians and Surgeons.

MEDIA IN THIS ARTICLE

FIGURE 1

FIGURE 1. *INCIDENCE OF HYPERURICEMIA IN A HYPERTENSIVE POPULATION (TOTAL OF 47 PER CENT).*

Forty-three per cent of patients with primary, 44 per cent with renal, and 75 per cent with malignant hypertension had elevations of serum uric acid.

FIGURE 2

FIGURE 2. *PROGRESSIVE INCREASE IN THE INCIDENCE OF HYPERURICEMIA IN 119 UNTREATED HYPERTENSIVE PATIENTS AS THE LEVEL OF THE BLOOD UREA NITROGEN ROSE TO VALUES EXCEEDING 41 MG. PER 100 ML.*

- **25-50% of untreated primary hypertension**
- **75% of pts. if the hypertension was malignant or if there was coexistent renal disease**

Cannon PJ, et al. NEJM, 1966

- **Frequency of HTN in adult pts. with asymptomatic hyperuricemia is *about 50 %.***
- ***About 60% - 65% of pts*. with gout have HTN.**
- **Western diet with increased frequency of HTN.**

Saggaiani F, et al. Metabolism, 1996
Johnson RJ, et al. Hypertension, 2003
Johnson RJ, et al. Semin Nephrol 2005

Uric acid elevation is increased secondary to hypertension

Causes of Hyperuricemia in HTN

Possible mechanisms

1) Increased net reabsorption of UA

- Diuretics use
- Insulin resistance
- Reduced renal blood flow

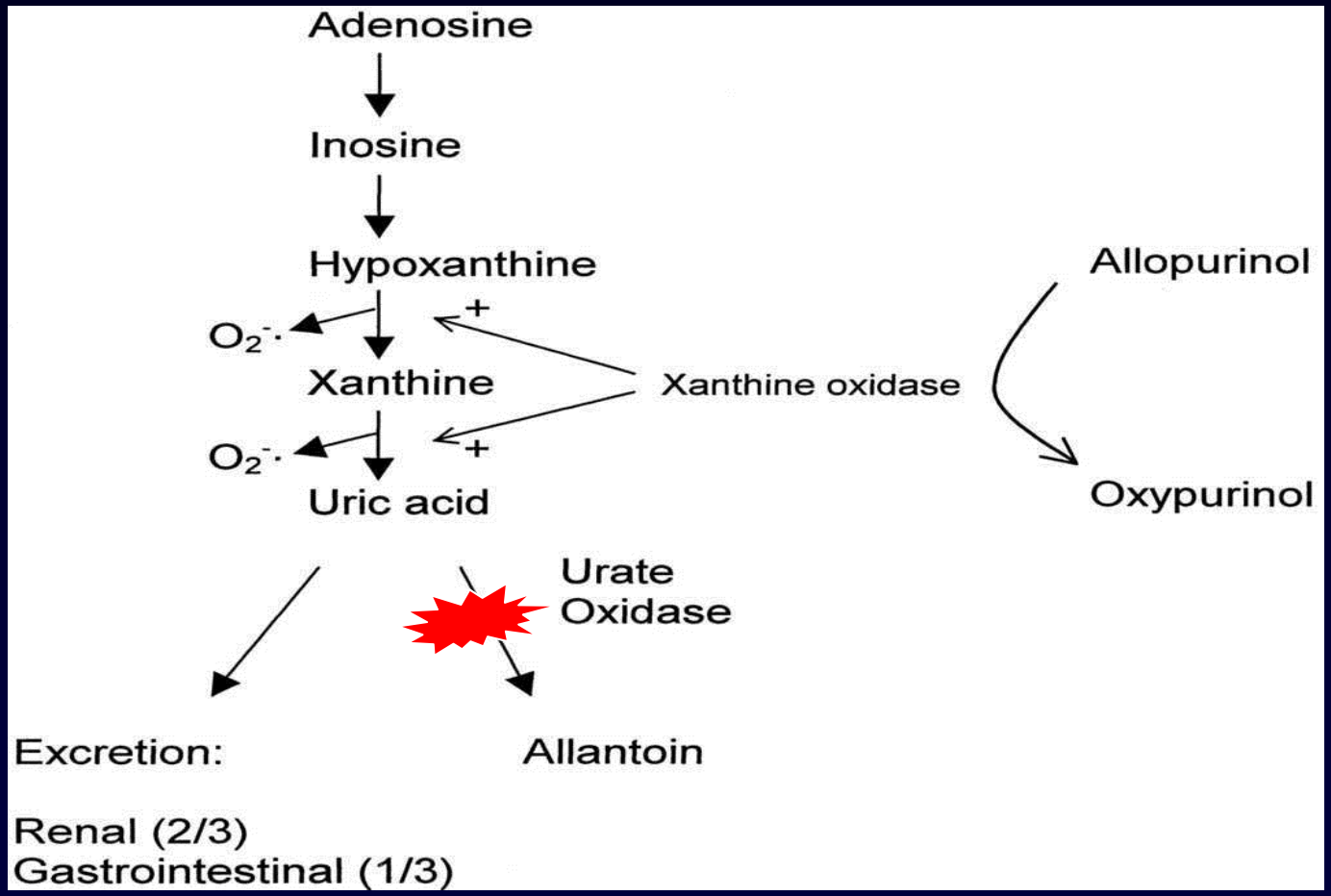
2) Decreased renal excretion

- Decreased renal excretion of UA d/t renal dysfunction
- Lactate competes with UA excretion

3) Increased production

- Increased activity of XO (endothelium)
- Increased conversion of XDH to XO
- Increased XO substrate resulting from increased adenosine and hypoxanthine

Pathophysiological Role of XO pathways in HTN



Hare, J. M. et al. Circulation 2003;107:1951-1953

Elevated uric acid predicts the development of hypertension

Table 3. Hyperuricemia and the Development of Hypertension.*

Study	No. of Patients	Relative Risk of Hypertension	95% CI
Kaiser Permanente, 1990[53]	2062 adults	2.1 times greater at 6 yr (high vs. low quintile)	1.20–3.98
University of Utah, 1991[44]	1482 adults	1.44 times greater per SD increment at 7 yr	1.03–2.01
Olivetti Heart, 1994[46]	619 men	1.23 times greater per 1 mg/dl increase at 12 yr	1.07–1.39
CARDIA, 1999[42]	5115 men	1.21 times greater per SD increment at 10 yr	1.03–1.41
Osaka Health Survey, 2001[56]	6356 men	2 times greater at 10 yr (high vs. low quintile)	1.56–2.60
Hawaii–Los Angeles–Hiroshima, 2001[45]	140 men	2.0 times greater at 15 yr (high vs. low quartile)	1.02–3.9
Osaka Factory, 2003[48]	433 men	1.0 mg/dl, increased 27 mm Hg SBP at 5 yr	Not calculated
Osaka Health Survey, 2003[51]	2310 men	1.13 times greater per SD increment at 6 yr	1.06–1.21
Okinawa, 2004[50]	4489 adults	1.46 times greater for men (uric acid ≥7 mg/dl) and 1.94 for women (uric acid ≥6 mg/dl) at 13yr	1.09–2.03 1.05–3.57
Bogalusa Heart, 2005[41]	679 children	Increased risk for diastolic hypertension at 11 yr	Not calculated
Framingham Heart, 2005[55]	3329 adults	1.17 times greater per SD increment at 4 yr	1.02–1.33
Normative Aging, 2006[52]	2062 men	125 times greater at 21 yr (uric acid >6.5 mg/dl)	1.08–1.34
ARIC, 2006[49]	9104 adults	1.1 times greater per SD increment at 9 yr	1.02–1.14
Beaver Dam Health Survey, 2006[54]	2520 adults	1.65 times greater at 10 yr (high vs. low quintile)	1.41–1.93
Health Professionals' Follow-up, 2006[43]	750 men	1.02 times greater per SD increment at 8 yr	0.92–1.13
MRFIT, 2007[47]	3073 men	1.1 times greater per SD increment at 6 yr	1.02–1.19

Feig D et al, NEJM, 2008

Prevalence of Hyperuricemia

- 2~35% in general population
- 25~50% of untreated primary hypertension
- 50% of hypertension on diuretics
- 70~100% of malignant hypertension
- ~ 50% in CKD at the onset of renal replacement therapy

According to Meta-analysis (N=55,607)

Hyperuricemia

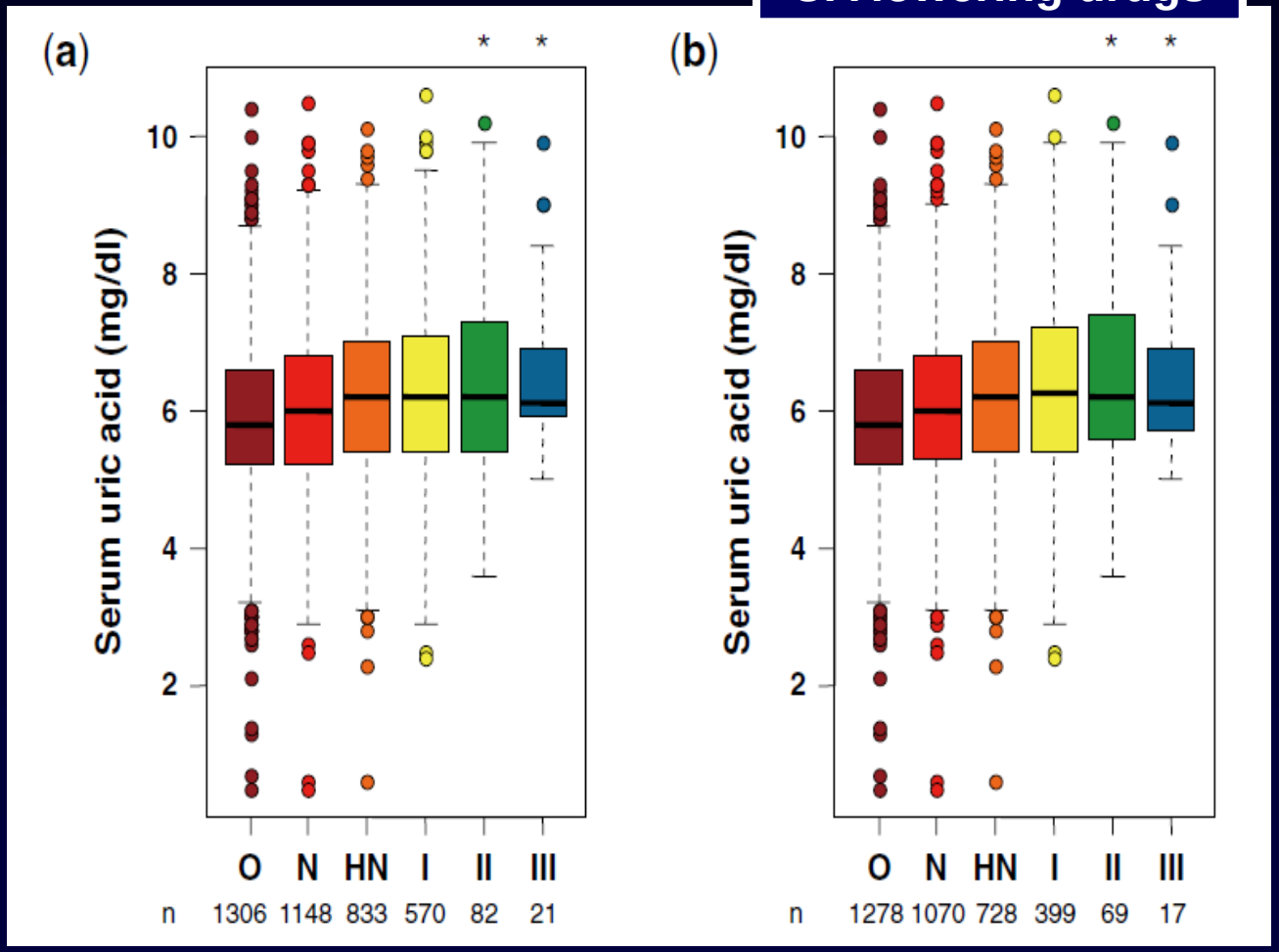
Risk of hypertension : 42 % ⬆

- **Increase of 1 mg/dl of UA ➔ risk of hypertension 13 %** ⬆
  - **Primary > Secondary HTN**
  - **Shorter duration of HTN > Longer duration**
  - **Younger > Older**
  - **Female > Male**

Grayson PC, et al. Arthritis Care Res 2011;63:102-10

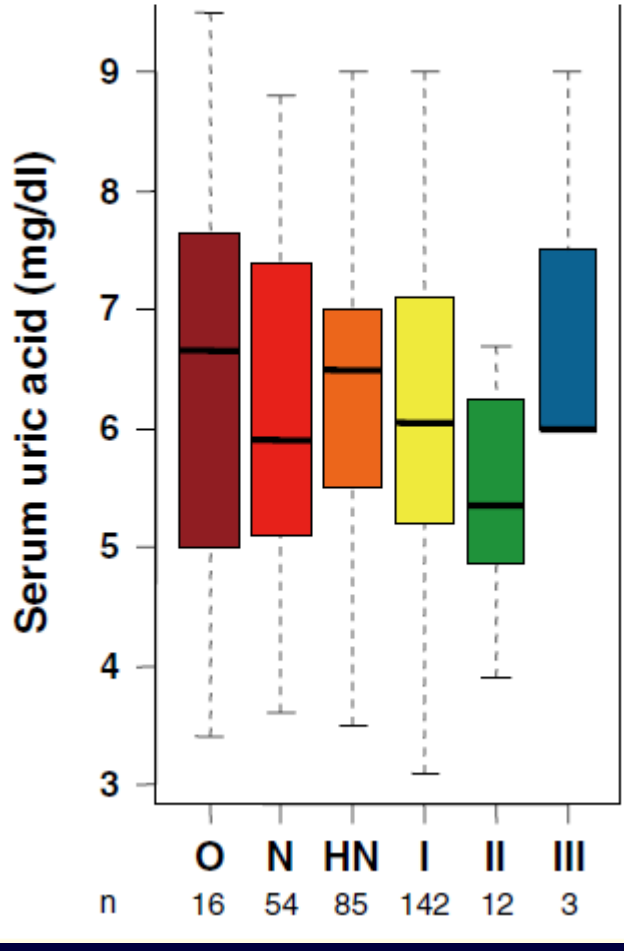
UA and Blood Pressure in Japanese Men

Study Subjects



Neither anti-HTN or UA lowering drugs

Subjects with anti-HTN but not UA lowering drugs



Kansui Y. et al. Circ J 2011;75:2827-2832

UA may play a role in the development of TOD in hypertension

Relationship between UA and PWV, IMT, albuminuria

PWV

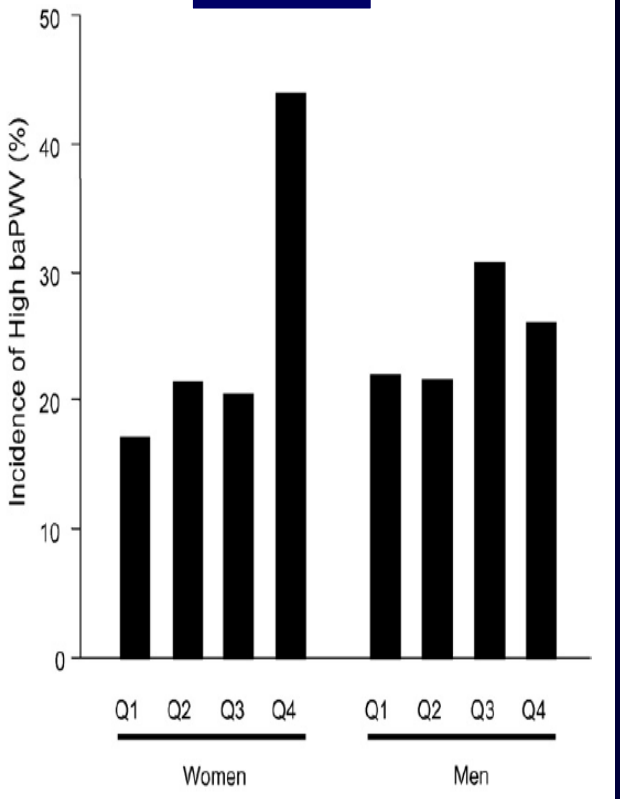


Fig. 1. Incidence of high baPWV according to the UA quartile and gender.

Ishizaka N, et al. Atheroscleroiss, 2007

Albuminuria

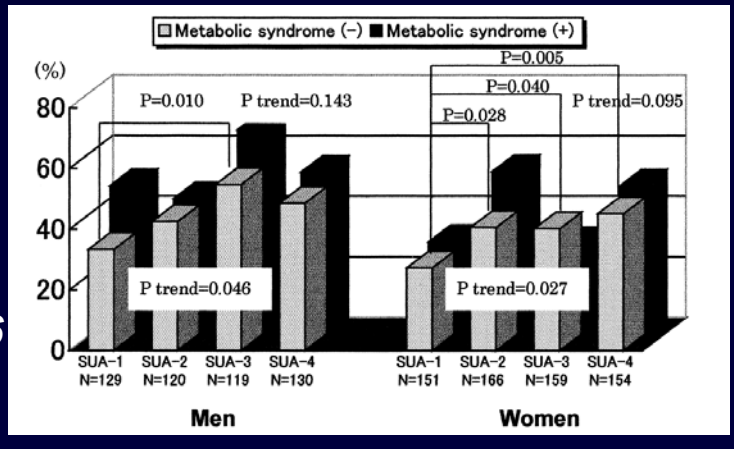
Table 3
Independent determinants of logarithm of urinary albumin excretion

	β	P
Duration of diabetes	.253	<.0001
HbA_{1c}	.166	.0034
Triglyceride	.125	.0472
Systolic blood pressure	.275	.0013
Uric acid	.281	<.0001

$R^2 = 0.252$ ($P < .0001$).

Fukui M, et al. Metabolism, 2008

IMT



Kawamoto R, et al. Internal Medicine, 2006

Relationship between UA and LVH

Table 2. Association Between UA Tertile and Prevalence of LVH by Multivariate Logistic Regression Analysis (n=3,305)

UA tertile	No. of LVH (%)	Crude		Model 1*		Model 2†	
		OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Lowest	155/1,109 (14.0)	1 (reference)	–	1 (reference)	–	1 (reference)	–
Middle	188/1,123 (16.7)	1.24 (0.98–1.56)	0.071	1.29 (1.02–1.64)	0.035	1.28 (1.01–1.63)	0.043
Highest	211/1,073 (19.7)	1.51 (1.20–1.89)	<0.001	1.61 (1.26–2.06)	<0.001	1.58 (1.23–2.02)	<0.001

*Adjusted for institute, age, BMI, HTN and log-transformed Creat.
†Adjusted for institute, age, BMI, HTN, DM, HL and log-transformed Creat.
OR, odds ratio. Other abbreviations see in Table 1.

Table 3. Association Between UA Tertile and the Prevalence of LVH in the Sample Stratified by Presence of HTN (n=3,305)

UA tertile	No. of LVH (%)	Normotensive group (n=2,652)			No. of LVH (%)	Hypertensive group (n=653)		
		OR* (95%CI)	P value	Trend P		OR* (95%CI)	P value	Trend P
Lowest	99/845 (11.7)	1 (reference)	–		54/212 (25.5)	1 (reference)	–	
Middle	134/899 (14.9)	1.35 (1.01–1.80)	0.04	0.022	54/226 (23.9)	0.93 (0.59–1.45)	0.74	0.021
Highest	135/908 (14.9)	1.43 (1.06–1.92)	0.020		78/215 (36.3)	1.68 (1.07–2.64)	0.025	

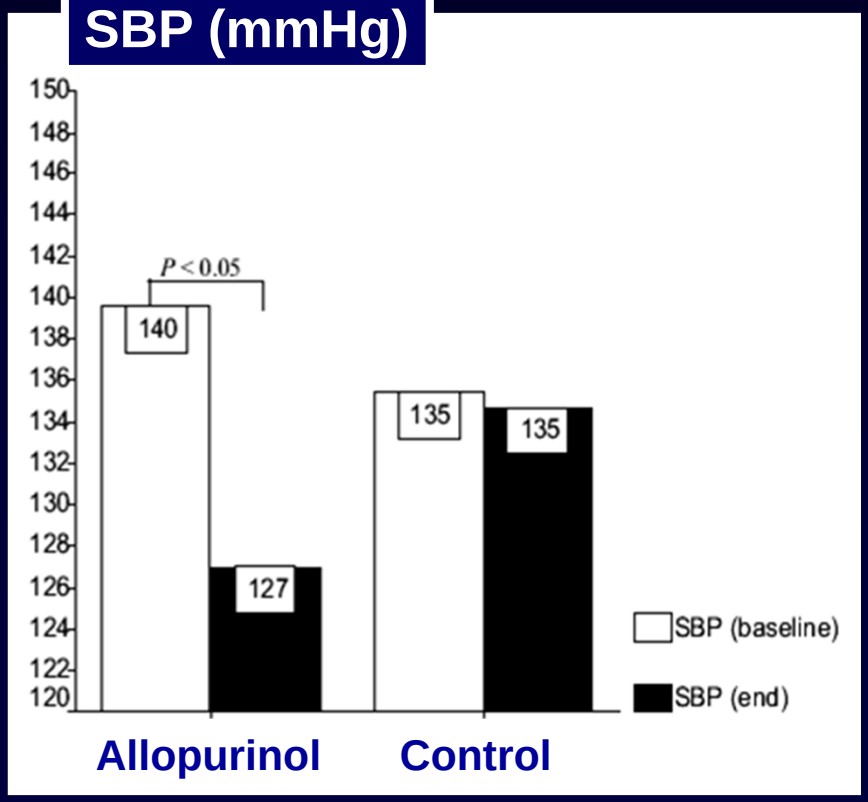
Normotensive defined as SBP<140 mmHg and DBP<90 mmHg; Hypertensive defined as SBP≥140 mmHg and/or DBP≥90 mmHg.
*Adjusted for institute, age, BMI, SBP, DM, HL and log-transformed Creat.
Abbreviations see in Tables 1,2.

Tsioufis C. et al. J Human Hypertension, 2005

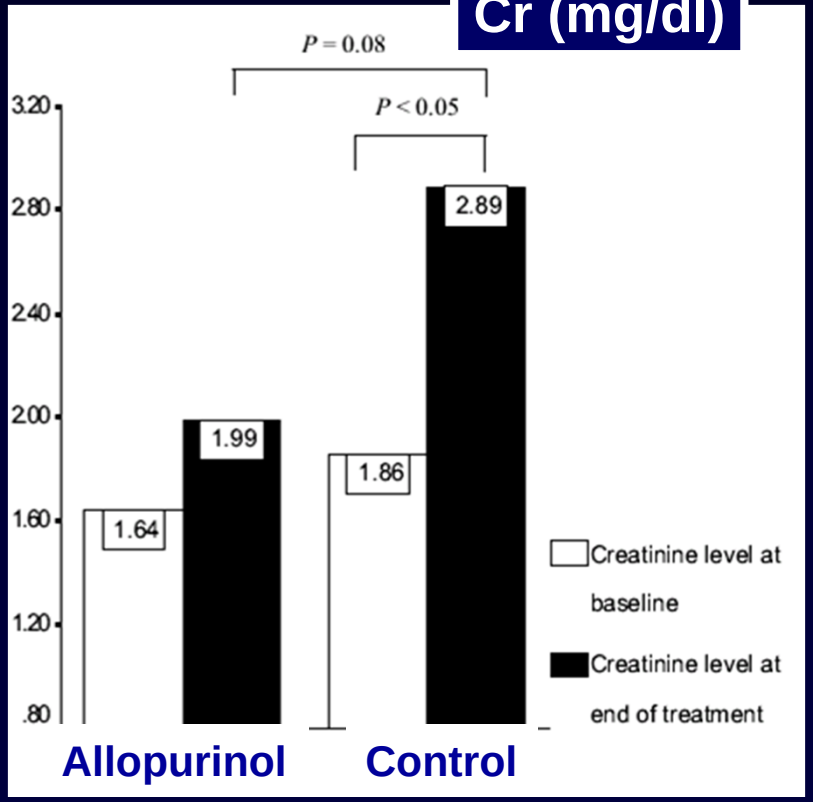
Use of Allopurinol in Slowing the Progression of Renal Disease Through Its Ability to Lower Serum Uric Acid Level

Yui-Pong Siu, MRCP, Kay-Tai Leung, MRCP, Matthew Ka-Hang Tong, MRCP, and Tze-Hoi Kwan, FRCP

SBP (mmHg)



Cr (mg/dl)



Am J Kidney Dis 47:51, 2006

UA is also related with CV diseases in hypertensive patients

Hyperuricemia predicts CV events : Studies of the Hypertensive Population

Study	Length of Follow-Up, y	Univariate Correlation with Events	Independent Predictor in Multivariate Analyses
Hypertension Detection Follow-Up Program Cooperative Research Group			
1985[36]	5	Yes	Yes
1987[37]	5†	Yes	Only women
Work site			
1999[38]	6.6	Yes	Yes
PIUMA (Progetto Ipertensione Umbria Monitoraggio Ambulatoriale)			
2000[39]	4	Yes	Yes
European Working Party on High BP in the Elderly			
1991[40]	3	Yes	No
SHEP (Systolic Hypertension in the Elderly Program)*			
2001[41]	5	Yes	Yes
Syst-China*			
2001[42]	3	Yes	Yes
Syst-Eur*			
2002[43]	2	No	No

*Patients with isolated systolic hypertension; †subanalysis of patients on thiazides.

Johnson RJ. et al. Hypertension 2003;41:1183-1190

Serum Uric Acid and Risk for Cardiovascular Disease and Death: The Framingham Heart Study

Bruce F. Culleton, MD; Martin G. Larson, ScD; William B. Kannel, MD; and Daniel Levy, MD

Background: Hyperuricemia is associated with risk for cardiovascular disease and death. However, the role of uric acid independent of established risk factors is uncertain.

Objective: To examine the relation of serum uric acid level to incident coronary heart disease, death from cardiovascular disease, and death from all causes.

Design: Community-based, prospective observational study.

Setting: Framingham, Massachusetts.

deaths, and 1460 deaths from all causes occurred. In men, after adjustment for age, elevated serum uric acid level was not associated with increased risk for an adverse outcome. In women, after adjustment for age, uric acid level was predictive of coronary heart disease ($P = 0.002$), death from cardiovascular disease ($P = 0.009$), and death from all causes ($P = 0.03$). After additional adjustment for cardiovascular disease risk factors, uric acid level was no longer associated with coronary heart disease, death from cardiovascular disease, or death from all causes. In a stepwise Cox model, diuretic use was identified as the covariate responsible for rendering serum uric acid a statistically nonsignificant predictor of outcomes.

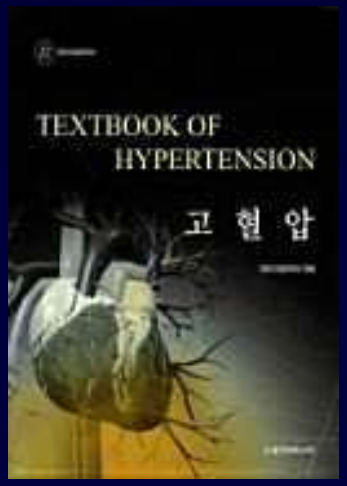
Conclusions: These findings indicate that uric acid does not have a causal role in the development of coronary heart disease, death from cardiovascular disease, or death from all causes. Any apparent association with these outcomes is probably due to the association of uric acid level with other risk factors.

The association of serum uric acid with cardiovascular disease has been appreciated for nearly half a century (1). Several prospective studies have shown an association between baseline hyperuricemia and incident coronary heart disease, cardiovascular disease, and death (2–10). Despite the strength of these associations, uric acid has not been established as a causal risk factor for cardiovascular disease. Instead, uric acid seems inextricably linked to hypertension, dyslipidemia, and disordered glucose

UA does not have causal role in the development of CHD, CV mortality and all-cause mortality

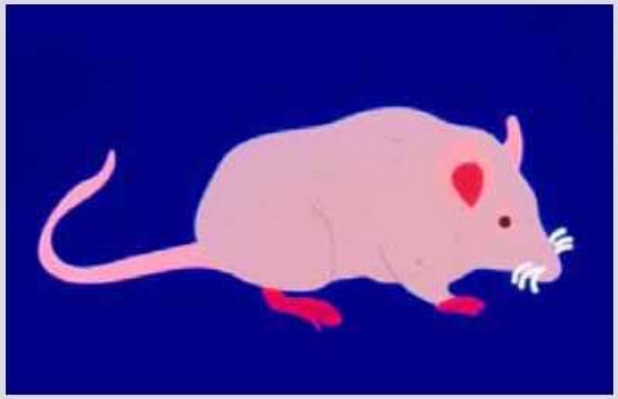
tion Study (NHANES I), Freedman and colleagues (3) demonstrated that each 60-μmol/L increment in uric acid level was associated with a 48% increase in risk for incident ischemic heart disease among women. Furthermore, a growing body of laboratory and clinical evidence suggests that uric acid plays a role in platelet adhesiveness (15–17), formation of free radicals (18), and oxidative stress (19, 20).

As a result of this growing controversy, we revisited this question in the Framingham Heart Study sample. Longer and more contemporary follow-up and more outcome events allowed us to expand on a previous Framingham report (2). In this paper, we describe the relation of baseline serum uric acid level to 1) incident coronary heart disease events (death from coronary heart disease, recognized myocardial infarction, and coronary insufficiency), 2) death from cardiovascular disease, and 3) death from



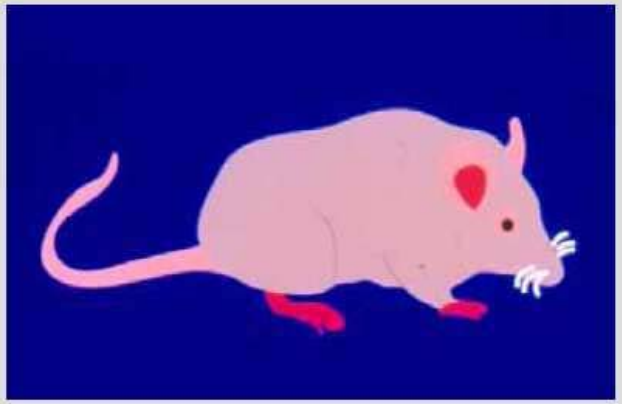
Experimental studies suggest a causal role for uric acid in hypertension

Animal Model of Mild Hyperuricemia



Uricase inhibitor

Oxonic acid (OA)



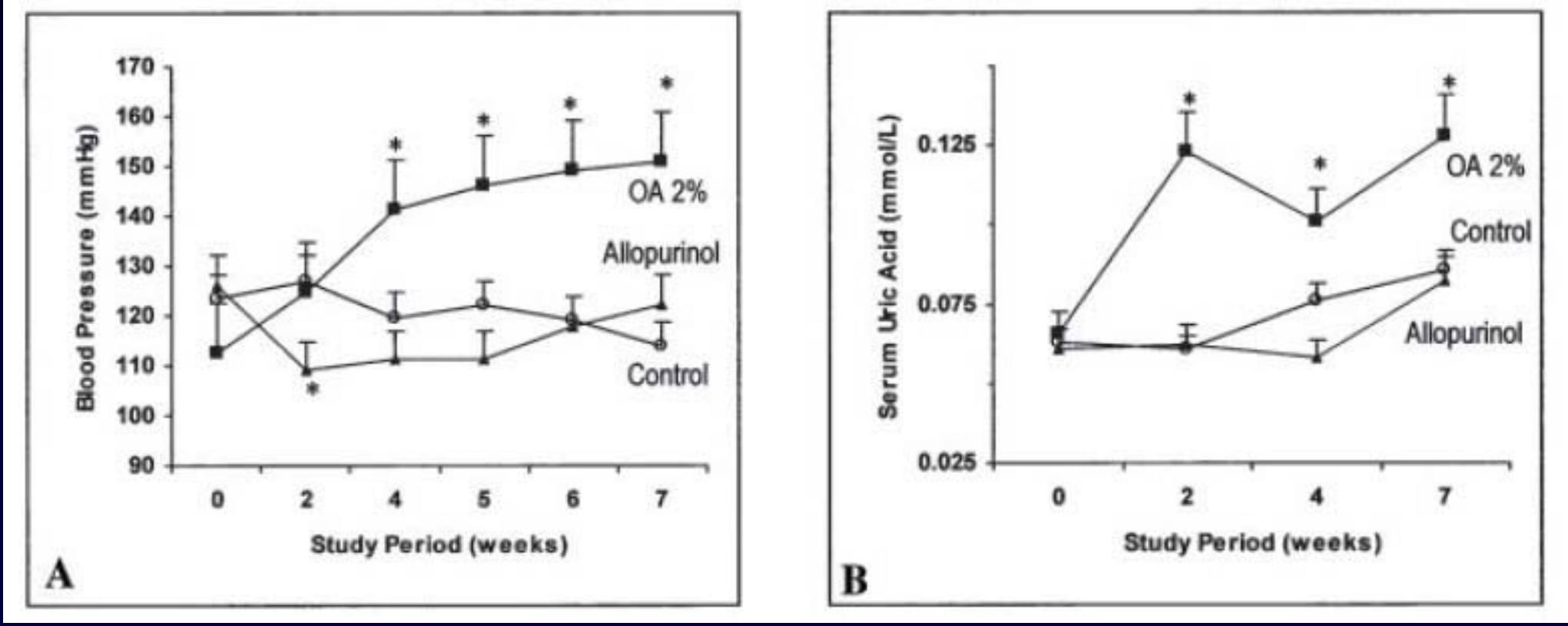
Normal Rat

Uric Acid (0.5-1.4 mg/dl)

Hyperuricemic Rat

Uric Acid (1.7-3.0 mg/dl)

Mazzali M, et al. Hypertension, 2001



Mazzali M, et al. Hypertension, 2001

Experimental studies - Renal hemodynamics

Hyperuricemic rats

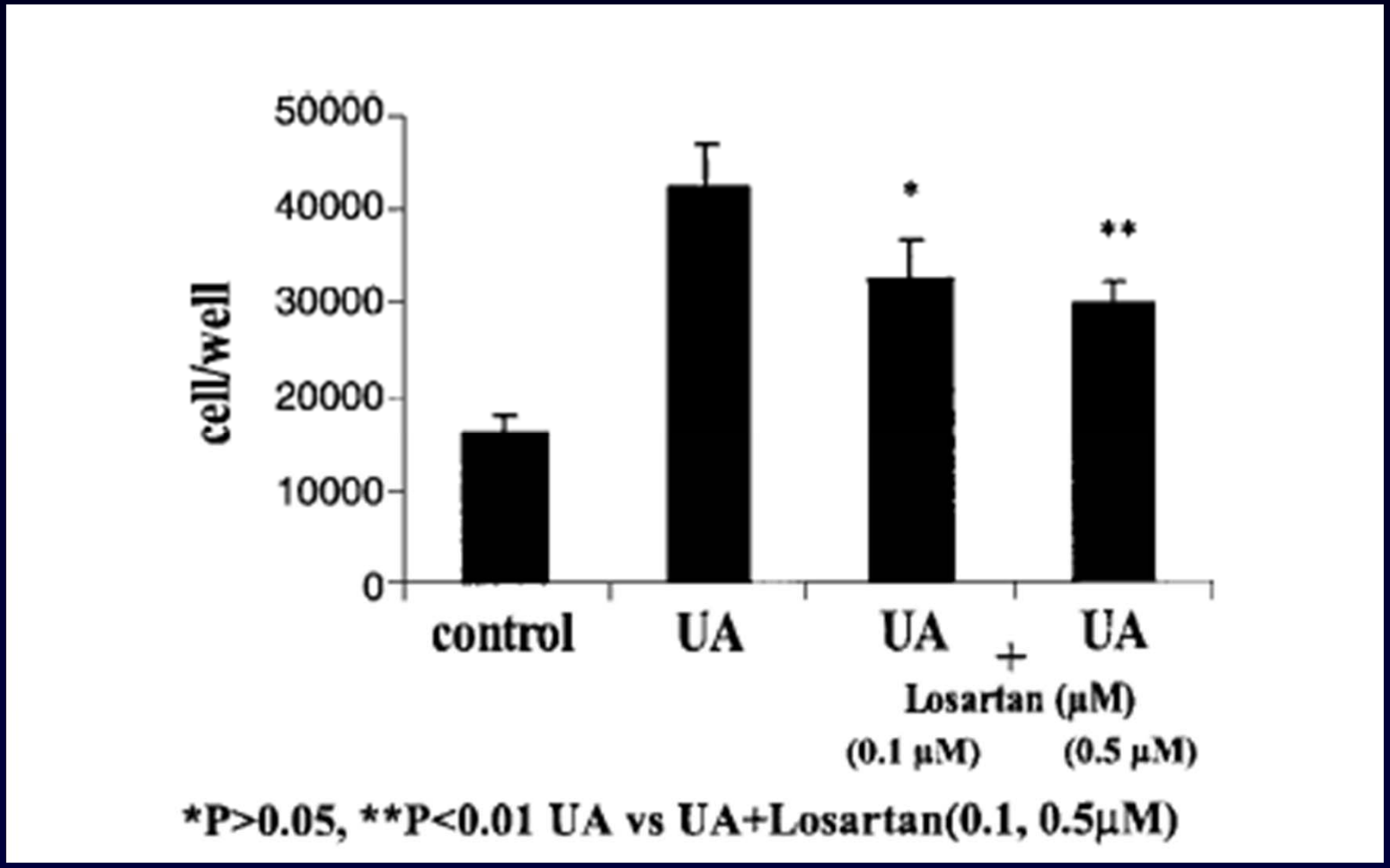
- A marked increase in glomerular hydrostatic pressure
- Increase in renal afferent arteriolar resistance
- Decrease in renal blood flow

- Associated with increased oxidative stress, endothelial dysfunction and RAS activation

Renal arteriolar microvascular disease, mild interstitial inflammation

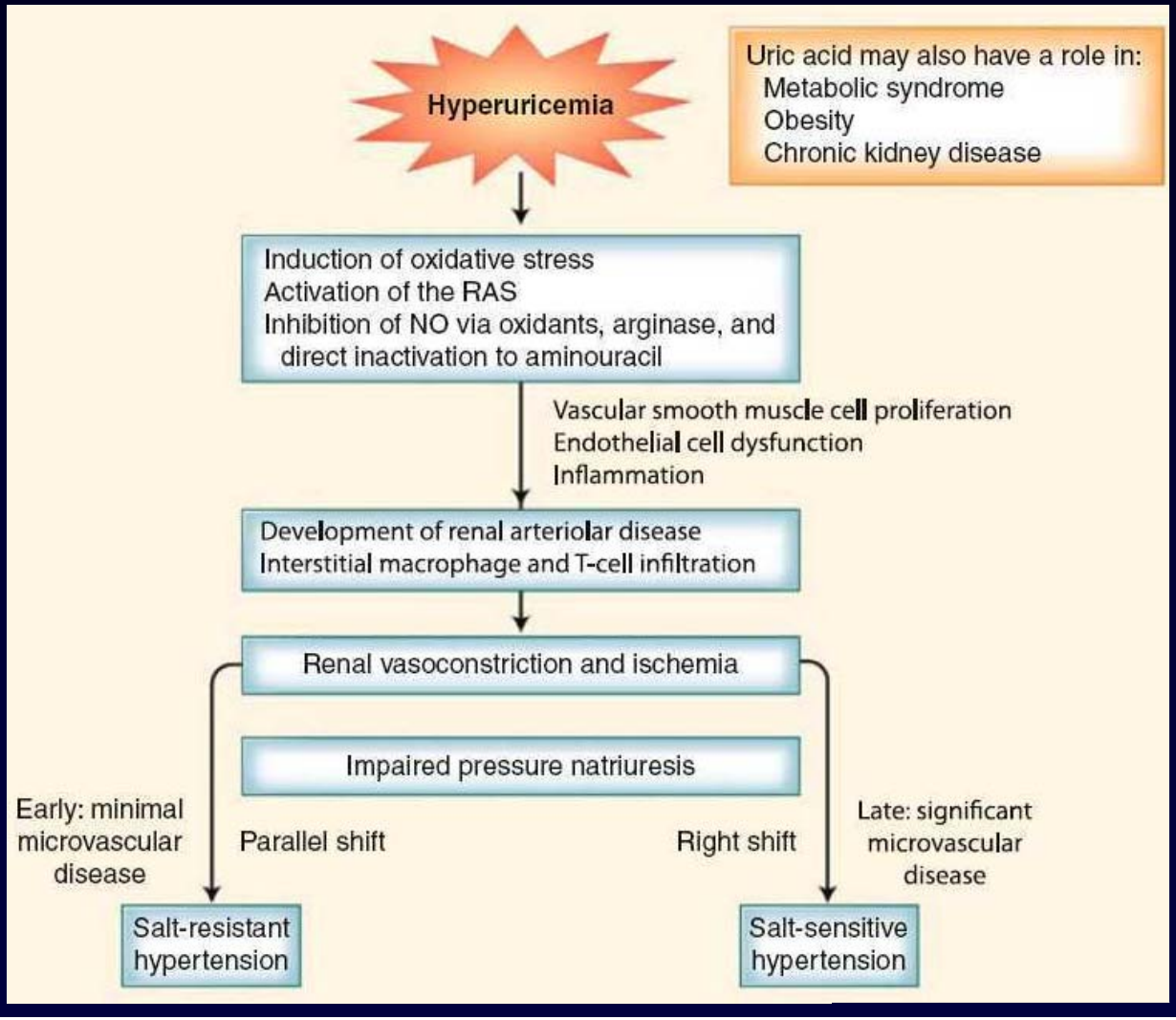
Mazzali M, et al. Am J Physiol, 2002

Effect of UA on VSMC proliferation



Mazzali M, et al. Am J Physiol, 2002

Proposed mechanism by which UA may cause HTN



Interventional studies have supported a role for UA in hypertension

Effect of treatment of hyperuricemia with allopurinol on blood pressure, creatinine clearence, and proteinuria in patients with normal renal functions

This was one of the first articles to show the potential effect of lowering UA on blood pressure

Table 2 Laboratory parameters and blood pressure measurements of the treatment and control groups

	Allopurinol group		Control group	
	Baseline	After 3 months	Baseline	After 3 months
Uric acid (mg/dl)	8.0 ± 0.76	5.5 ± 1.2*	5.8 ± 0.2	5.8 ± 0.0
Creatinine (mg/dl)	1.24 ± 0.36	1.14 ± 0.32*	1.1 ± 0.0	1.09 ± 0.4
Glomerular filtration rate (ml/min)	79.2 ± 31.9	92.9 ± 36.8*	89.4 ± 3.0	91.0 ± 6.1
C-reactive protein (mg/l)	2.8 ± 1.4	2.5 ± 1.3*	2.6 ± 1.6	2.4 ± 1.5
Urine protein (mg/day)	134.5 ± 132.0	131.5 ± 108.1	111.0 ± 17.5	114.6 ± 12.9
Systolic blood pressure (mmHg)	135.4 ± 4.6	131.5 ± 4.1*	133.2 ± 6.9	132.6 ± 7.9
Diastolic blood pressure (mmHg)	80.2 ± 6.2	78.3 ± 3.1*	82.1 ± 5.6	80.8 ± 6.4

*$P < 0.05$

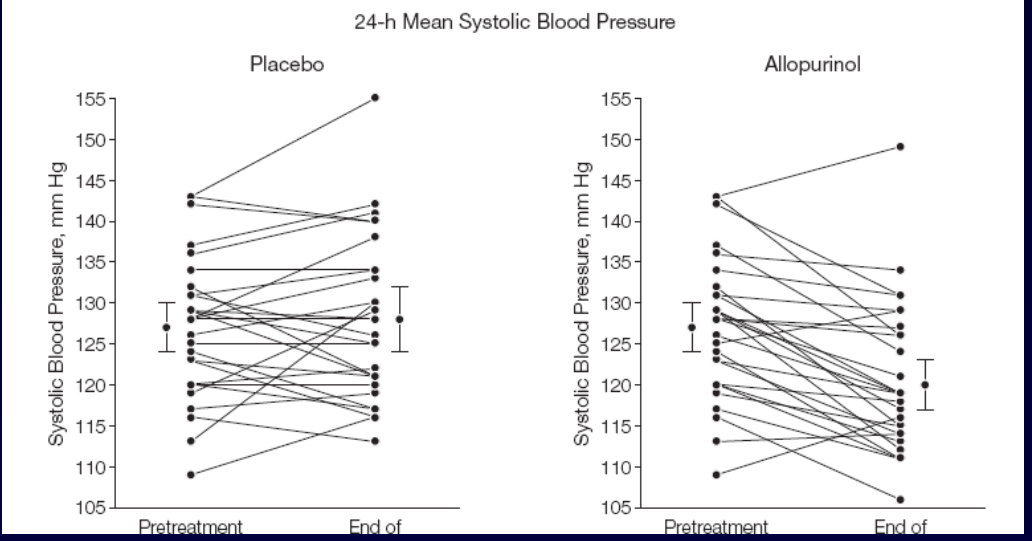
Kanbay M, et al. Int Urol Nephrol, 2007

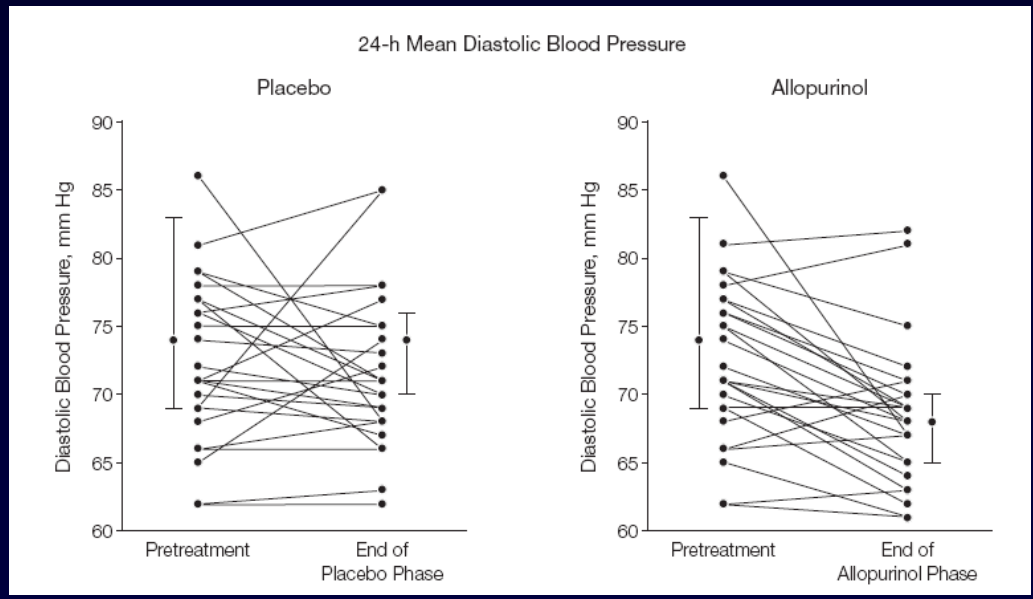
Effect of Allopurinol on Blood Pressure of Adolescents With Newly Diagnosed Essential Hypertension

A Randomized Trial

This was the first placebo-controlled trail to show an effect of lowering UA on blood pressure

Figure 2. Blood Pressure Response of Adolescents to Allopurinol and Placebo





Feig DI, et al. JAMA, 2008

EFFECT OF ALLOPURINOL IN CHRONIC KIDNEY DISEASE (CKD) PROGRESSION AND CARDIOVASCULAR RISK

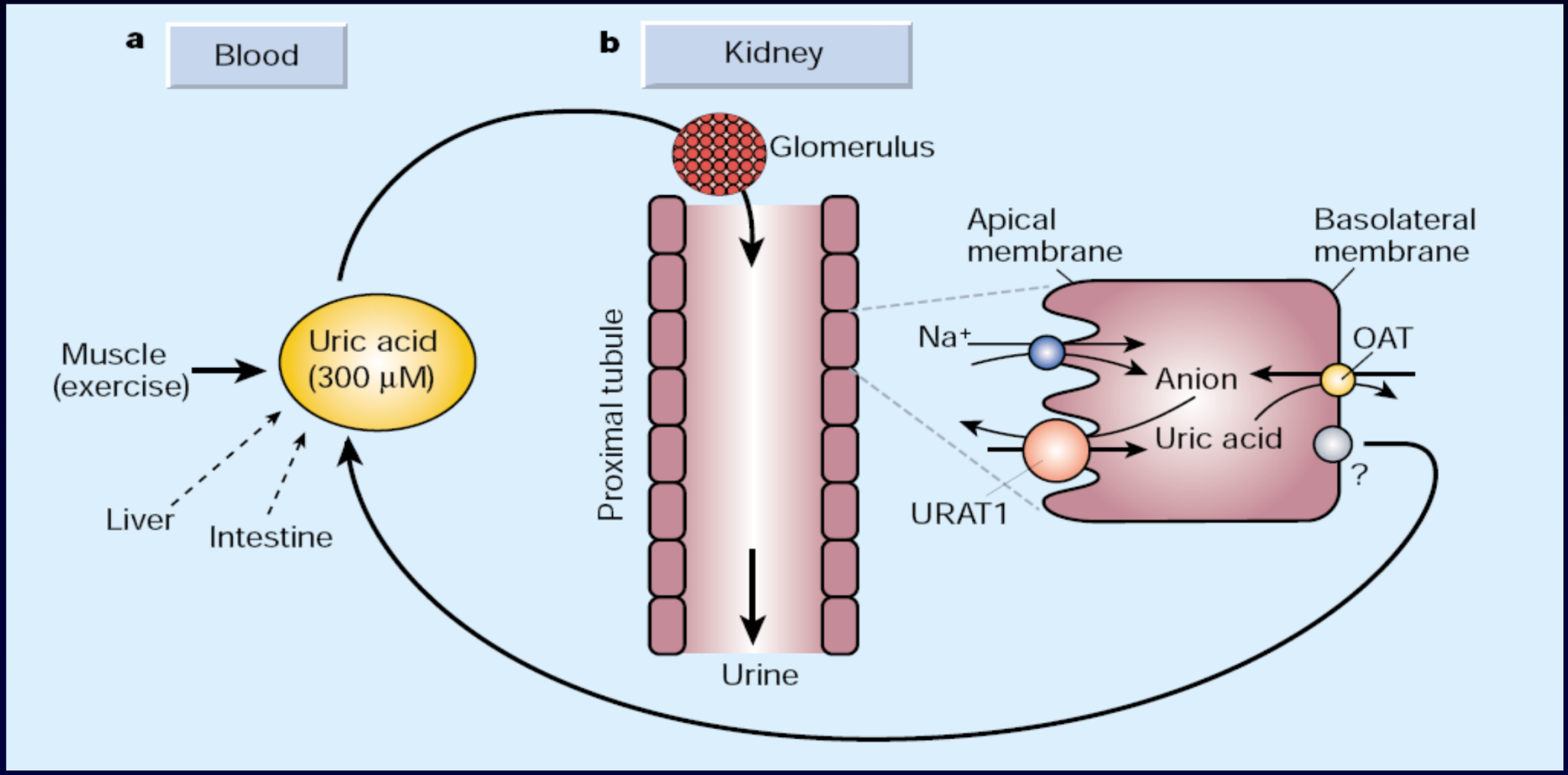
- 113 CKD patients with eGFR<60 ml/min
- Allopurinol 100 mg/day vs. placebo
- 12 months

		Uric acid* (mg/dl)	hsPCR** (mg/l)	C cystatin[1] (mg/l)	albuminuria (mg/day)	fibrinogen (mg/dl)
Control group	Basal	7.3±1.6	3.4(5.2)	2.0±0.7	32(383)	384±104
	6 months	7.0±1.6	3.0(7.6)	2.0±0.8	43(417)	373±112
	12 months	7.4±2.0	3.2(10.8)	1.9±1.0	51(296)	402±98
Allopurinol group	Basal	7.8±2.1	4.4(4.5)	1.9±0.5	36(388)	381±78
	6 months	6.2±1.5	3.0(4.0)	1.8±0.6	15(103)	367±58
	12 months	6.0±1.8	3.0(2.5)	1.4±0.4	16(166)	369±49

* p=0.016 between groups and time periods (two-way ANOVA)
** p=0.018 between groups and time periods (two-way ANOVA)
[1] p=0.008 between groups (two-way ANOVA)

Goicoechea M et al, CJASN

Pathways for Uric Acid Transport



Hediger, Nature 2002

Uricosuric Action of Losartan via the Inhibition of Urate Transporter 1 (URAT1) in Hypertensive Patients

Toshihiro Hamada[1], Kimiyoshi Ichida[2], Makoto Hosoyamada[3], Einosuke Mizuta[1], Kiyotaka Yanagihara[1], Kazuhiko Sonoyama[1], Shinobu Sugihara[1], Osamu Igawa[1], Tatsuo Hosoya[4], Akira Ohtahara[5], Chiaki Shigamasa[1], Yasutaka Yamamoto[6], Haruaki Ninomiya[7] and Ichiro Hisatome[6]

BACKGROUND

The angiotensin receptor blocker losartan inhibited urate transporter 1 (URAT1) according to *in vitro* experiments. However, it is still unknown whether the inhibitory effect of losartan on URAT1 contributes to its uricosuric action in humans.

METHODS

Thirty-two patients with hypertension and nine patients with idiopathic renal hypouricemia (five with and four without hypertension) were enrolled for this study. Hypertensive patients were prescribed oral losartan (50 mg/day, $n = 16$) or candesartan (8 mg/day, $n = 16$). Before and after 1-month treatment, the serum concentration of urate (Sur) and creatinine (Scr), and the clearance value of urate (Cur) and creatinine (Ccr) were determined. Clearance studies using the URAT1 inhibitor benzbromarone (100 mg/day) or losartan (50 mg/day) loading test were also performed in these patients.

RESULTS

Blood pressure (BP) significantly decreased in the patients treated with either losartan or candesartan. Losartan significantly reduced Sur, which was associated with a concomitant increase in the Cur/Ccr ratio, whereas candesartan did not alter these parameters. In hypertensive patients with loss-of-function mutation of URAT1, losartan did not alter either Sur or Cur/Ccr, nor did benzbromarone. The lack of effect of URAT1 inhibitors on renal excretion of urate was independent of the renal function of hypouricemic patients. On the other hand, both losartan and benzbromarone increased Cur/Ccr ratio in hypertensive patients harboring the wild *URAT1* gene, regardless of the presence of hypouricemia.

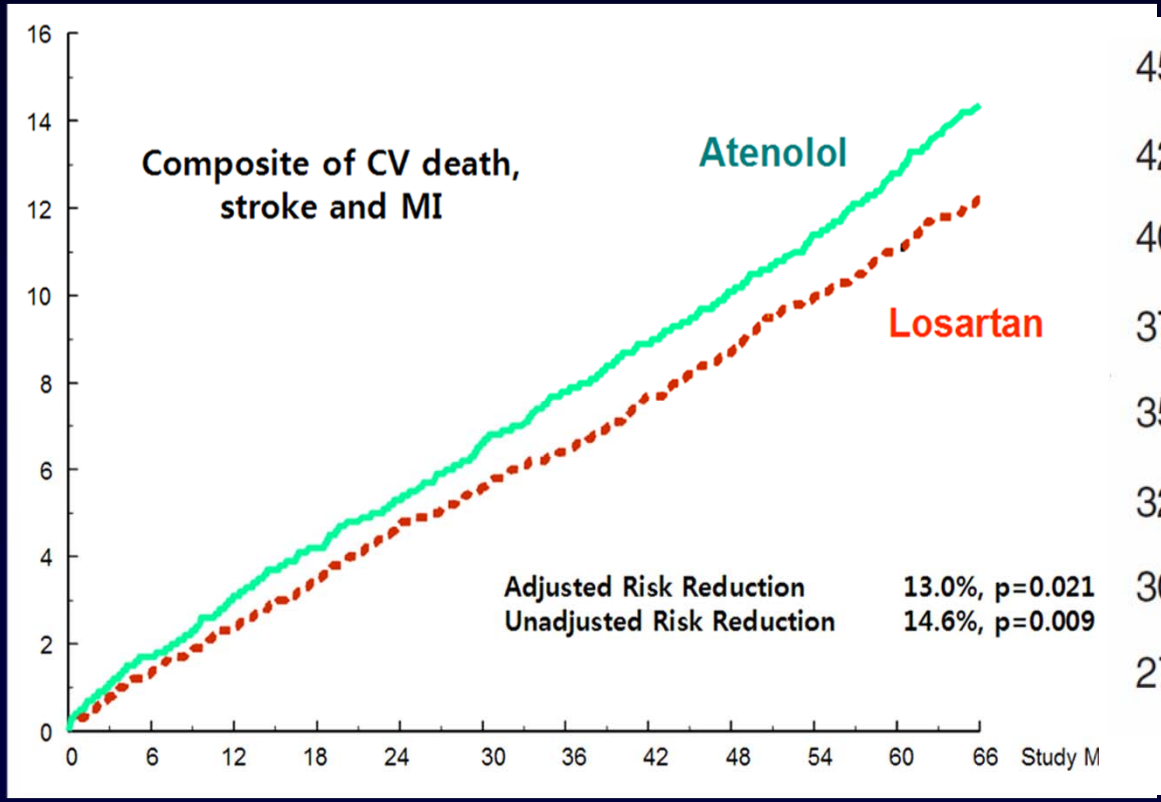
CONCLUSIONS

These findings suggested that losartan inhibited URAT1 and thereby it lowered Sur levels in hypertensive patients.

Am J Hypertens 2008; **21**:1157-1162 © 2008 American Journal of Hypertension, Ltd.

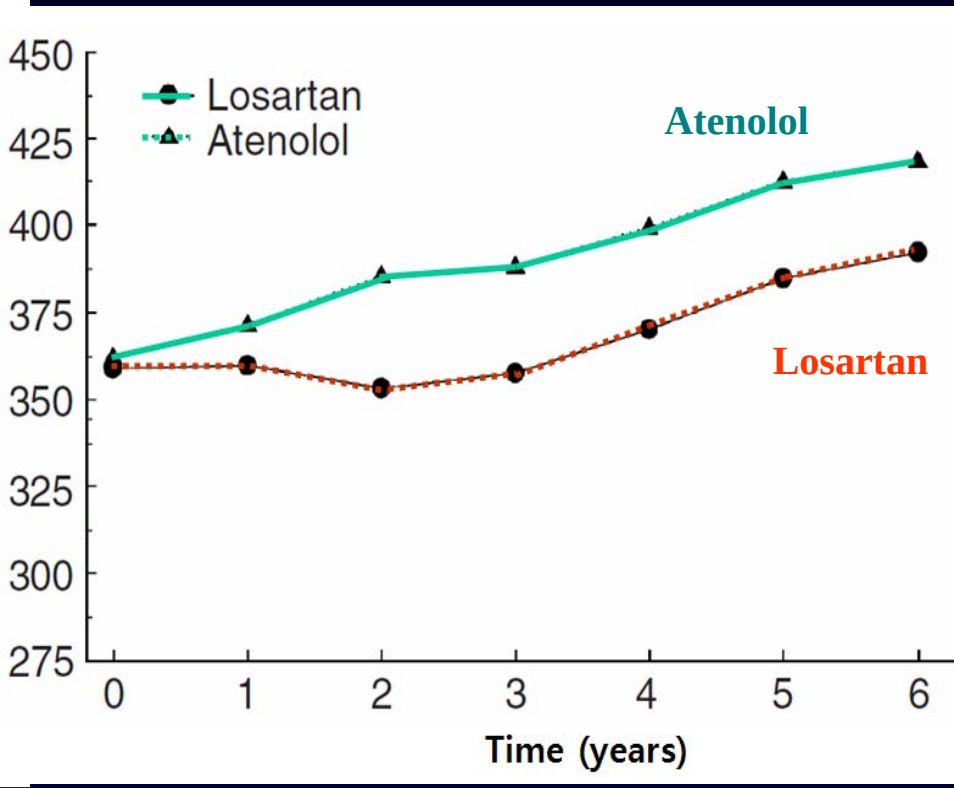
Role of Uric Acid in Cardiovascular Morbidity & Mortality: LIFE Study

Proportion of patients with first event(%)



Dahlöf B et al, *Lancet* 359:995, 2002

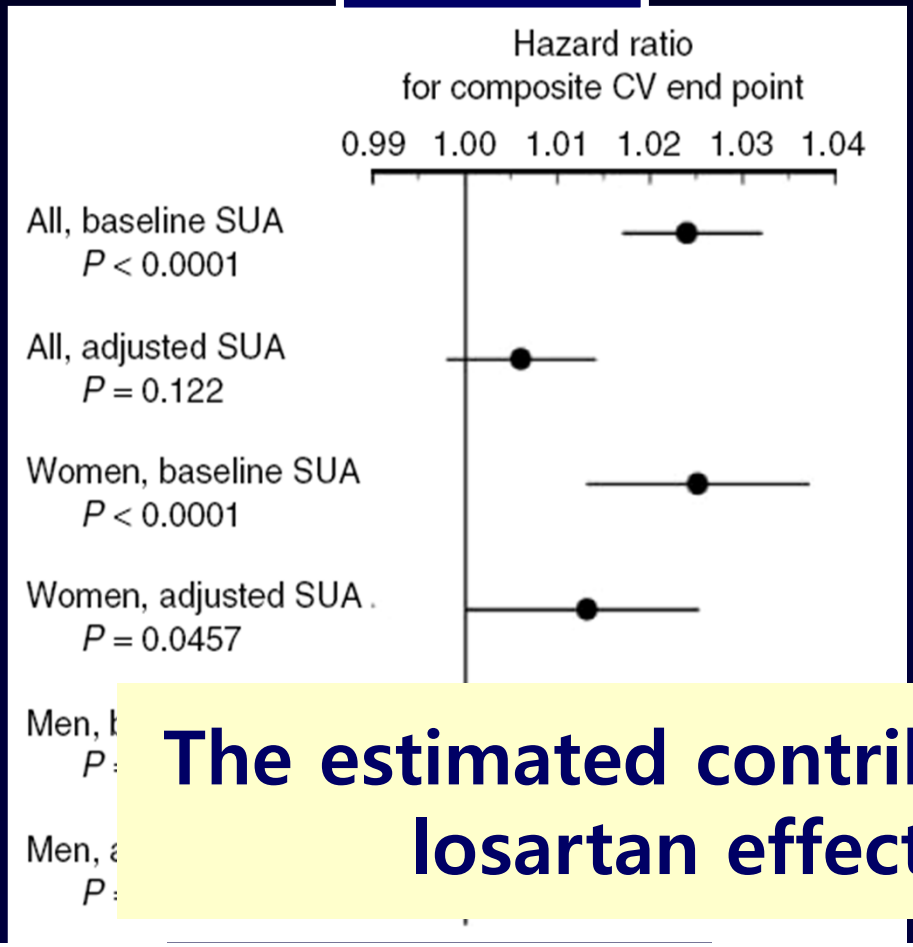
Serum uric acid (μM/L)



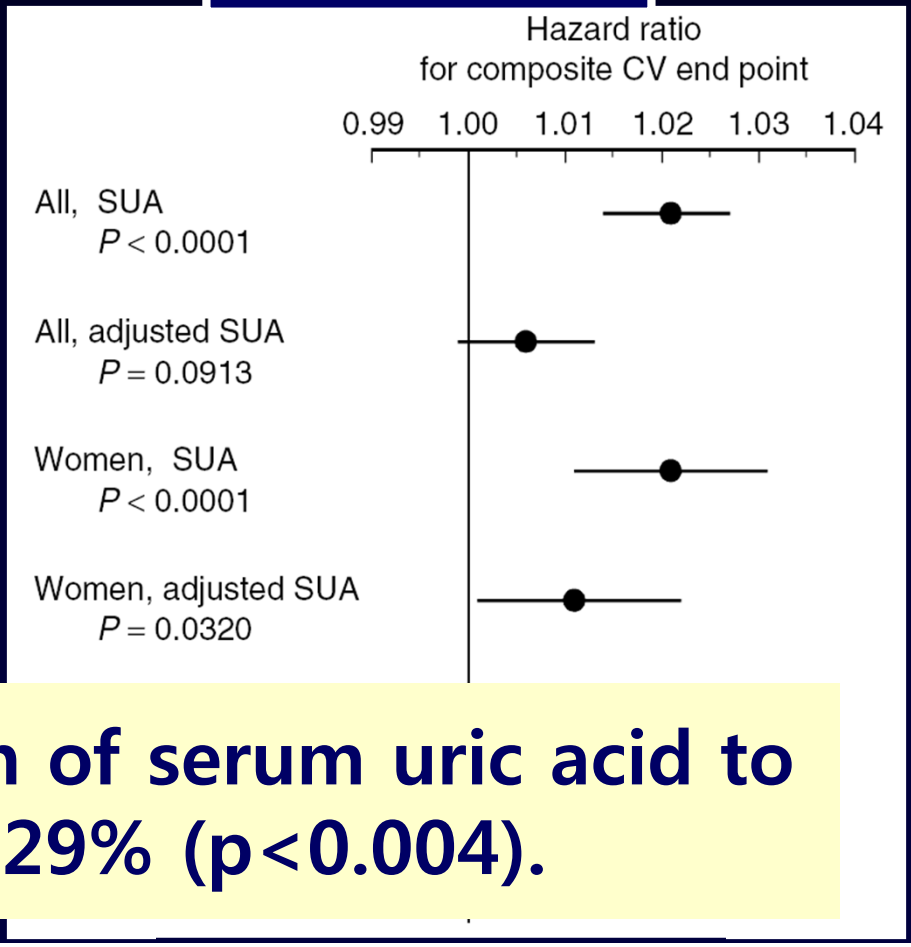
Hoieggen A et al, Kidney Int 65:1041, 2004

Impact of Serum Uric Acid on CV Outcome : LIFE Study

Baseline

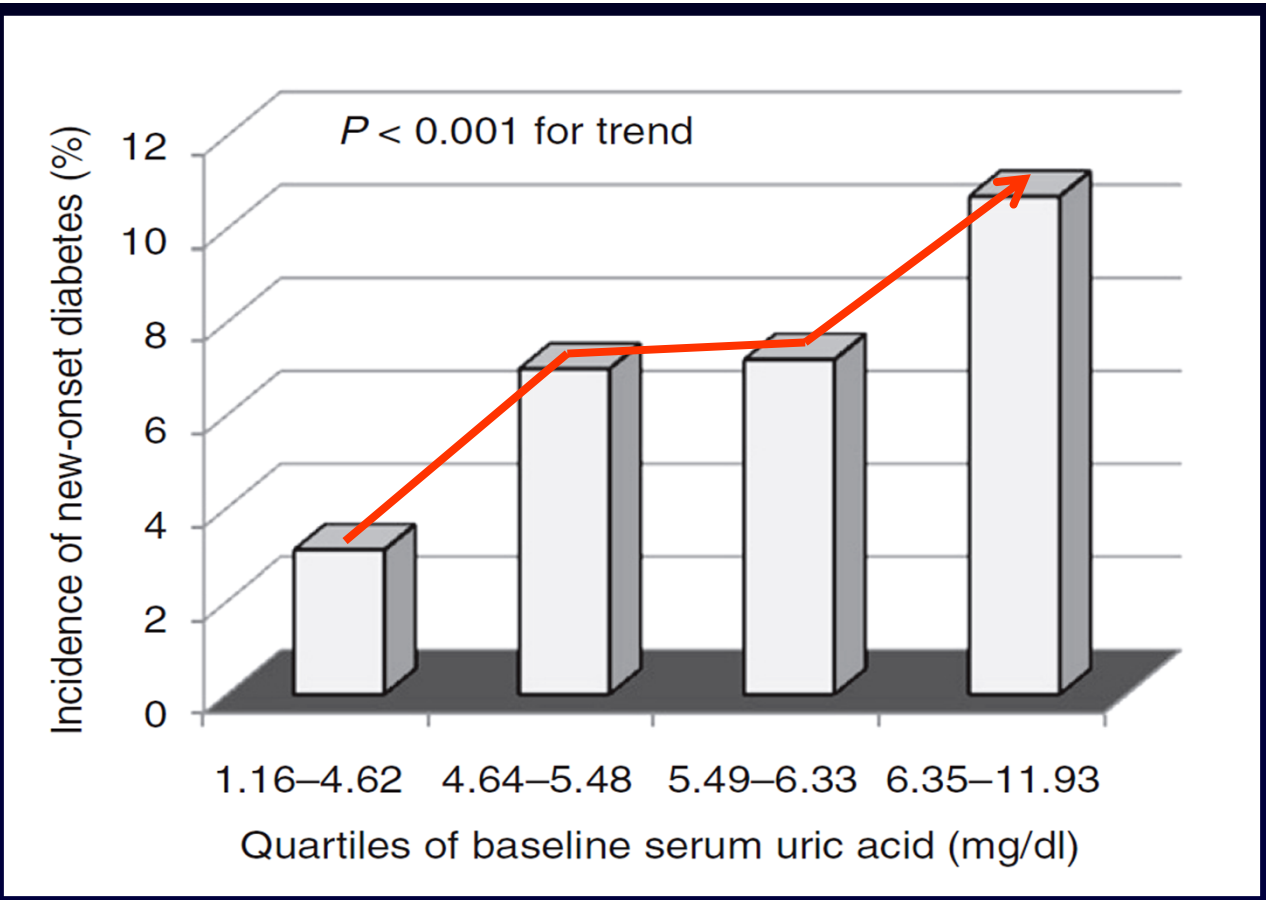


On-treatment



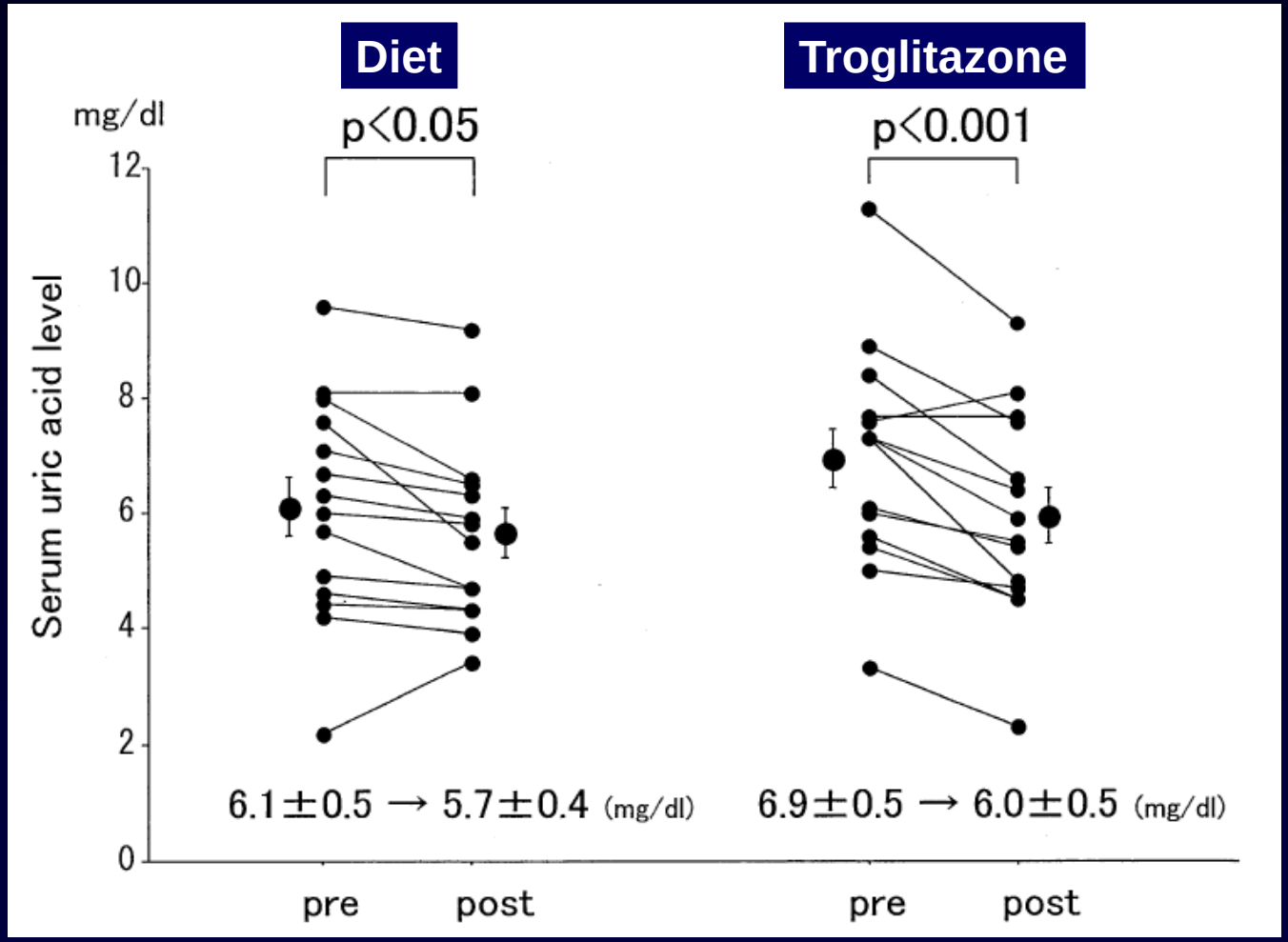
The estimated contribution of serum uric acid to losartan effect was 29% (p<0.004).

Serum Uric Acid Is Associated With New-Onset Diabetes in Hypertensive Patients With Left Ventricular Hypertrophy: The LIFE Study

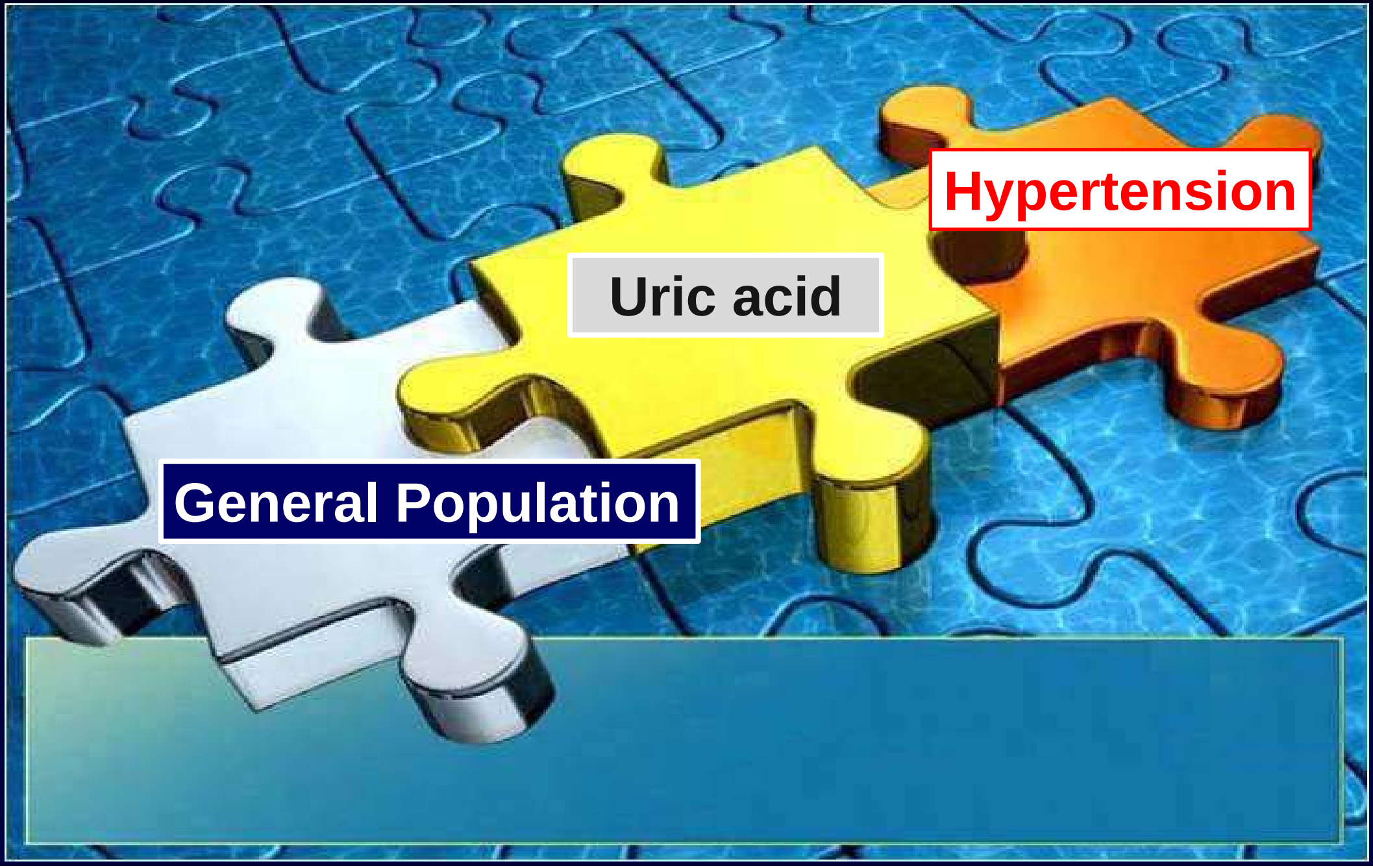


Wiik BP et al, Am J Hytertens, 2010

Lifestyle modification & Insulin-sensitizing agents



Tsunoda S. et al. Am J Hypertens 2002;15:697-701


Hypertension
Uric acid
General Population

Uric acid paradox

UA, as an antioxidant

- **This concept is supported by the superior performance of antihypertensive therapy with *thiazide diuretics* in preventing heart failure**

ALLHAT Study, JAMA, 2002

- ***Possible mechanism***
  - **Different role between intracellular(pro-oxidant, NADPH oxidase) and extracellular UA(antioxidant)**

UA, as an antioxidant

- **UA can function as an *antioxidant***
  - by scavenging various reactive oxygen species, itself
  - by promoting SOD activity

- **Systemic UA administration**
  - Increase plasma antioxidant capacity at rest
  - Reduce exercise-associated oxidative stress
  - Improve endothelial dysfunction

Still Controversy…

Benefits of lowering UA is due to..

Reduction of UA per se !

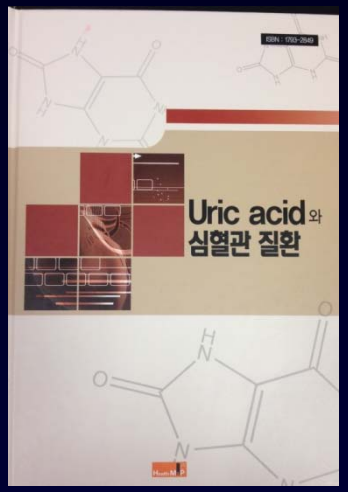
VS.

XO inhibitors with related reduction of ROS

The bottom line is…

- *Increasing evidence indicates that UA may have a causal role in HTN*
- **However, more studies are needed to dissect out the potential mechanisms**
- **Need more clinical trials to confirm a benefit of lowering UA on blood pressure**

경청해 주셔서 감사합니다



[論語(논어) 雍也篇(오야편)의 '어진 사람은 산을 좋아하고 지혜로운 사람은 물을 좋아한다.'는 知者樂水 仁者樂山(지자요수 인자요산)의 줄임 말이다.